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One-Pot Synthesis of α-Aminophosphonates Catalyzed by Boric Acid at Room Temperature

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ABSTRACT: *A simple, efficient, and general method has been developed for the one-pot, three-component synthesis of α-aminophosphonates from a condensation reaction of trimethyl phosphite, aldehydes, and amines in the presence of catalytic amount of boric acid (10 mol%) under solvent-free conditions. Thus α-aminophosphonates were synthesized relatively quickly in good yields at room temperature.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:96–98, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20577

INTRODUCTION

Multicomponent coupling reactions have emerged as powerful tools in combinatorial chemistry for the generation of small-molecule libraries. The goal is to aid the discovery of new leads for drug development and optimization of processes or to identify novel biologically active substrates. Multicomponent reaction condensations involve three or more compounds reacting in a single event, but consecutively to form new products, which contain the essential parts of all the starting materials [1].

α-Aminophosphonates are attractive targets for chemical synthesis because of their wide use as biologically active molecules. Their diverse applications include as antibiotics [2], pharmacological agents [3], peptide mimics [4], enzyme inhibitors [5], and as surrogates of α-amino acids [6].

Various methods are available for the construction of α-aminophosphonates [7]. One-pot three-component condensation of aldehydes, amines, and dimethylphosphite or trimethylphosphite is the most convenient method for the preparation of these compounds. In this context, some methods and catalysts have been reported such as $LiClO_4$ [8], oxalic acid [9], $TaCl_5$–SiO_2 [10], β-cyclodextrin [11], $Mg(ClO_4)_2$ [12], $InCl_3$ [13], SmI_2 [14], amberlite-IR 120 [15], $H_3PW_{12}O_{40}$ [16], ionic liquid [17], $FeCl_3$ [18], and silica sulfuric acid [19]. However, these methodologies show varying degrees of success as well as limitations due to use of toxic organic solvents, expensive catalyst, prolonged reaction times, the requirement of special apparatus, or harsh reaction conditions. Thus, there is a certain need for the development of an alternative route for the production of α-aminophosphonates, which surpassed those limitations.

RESULTS AND DISCUSSION

Following our systematic studies directed toward the development of practical, safe, and environmentally friendly procedures for several important organic transformations [20–22], we describe an efficient method for the synthesis of α-aminophosphonates through three-component reactions of aldehydes, amines, and trimethyl phosphite using catalytic amounts of boric acid under solvent-free conditions at room temperature (Scheme 1).

Boric acid (H_3BO_3) is a useful and environmentally benign catalyst that has been successfully

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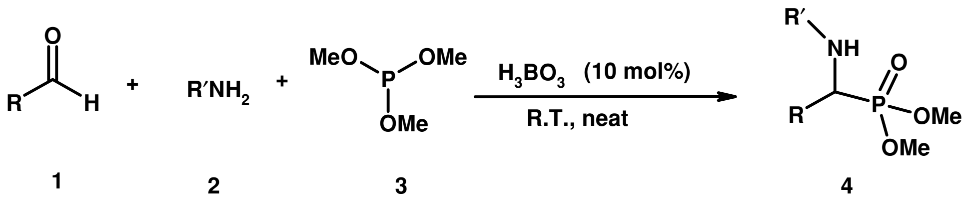


SCHEME 1 Synthesis of α-aminophosphonates.

utilized in numerous reactions, for example, the aza Michael addition [23], the thia Michael addition [24], Biginelli reaction [25], transesterification of ethyl acetoacetate [26], decarboxylation of cyclic β-enaminoketoesters [27], and Mannich reaction [28]. It offers milder conditions relative to common mineral acids. Boric acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture. Thus, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the synthesis of α-aminophosphonates.

To optimize the reaction conditions, the reaction of trimethyl phosphite with imine generated in situ from benzaldehyde and aniline was used as a model reaction. Reactions at different conditions and various molar ratios of substrates in the presence of boric acid revealed that the best conditions were solvent-free at room temperature and a molar ratio of trimethyl phosphite/amine/aldehyde/boric acid of 1:1:1:0.1. After completion of the reaction, the catalyst (boric acid) can be separated from the reaction mixture by washing the product with water.

To show the generality of this method, the optimized system was used for the synthesis of other α-aminophosphonate derivatives **4a–i** (Table 1).

This method offers some advantages in terms of simplicity of performance, solvent-free condition, and low reaction time. Several examples illustrating this novel and general method for the synthesis of α-aminophosphonates are summarized in Table 1. All products are known compounds, and their structures were confirmed by comparison with their known physical and spectral (NMR and IR) data.

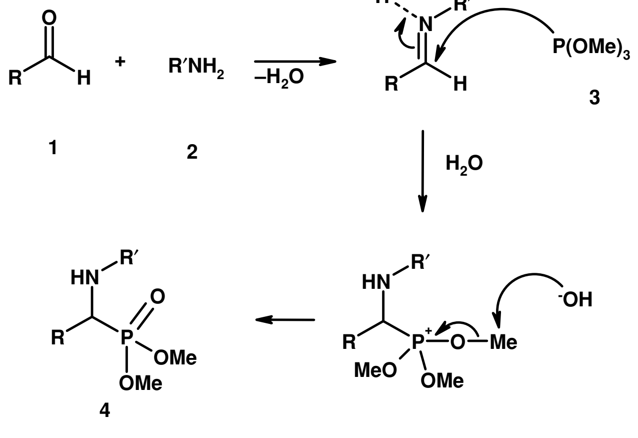
TABLE 1 Synthesis of α-Aminophosphonates in the Presence of 10 mol% of Boric Acid

	R	*R′*	*Time (min)*	*Yields (%)*
a	C_6H_5	Phenyl	15	98
b	4-ClC_6H_4	Phenyl	15	96
c	4-$NO_2C_6H_4$	Phenyl	15	98
d	4-MeC_6H_4	Phenyl	15	90
e	4-HOC_6H_4	Phenyl	15	87
f	4-CNC_6H_4	Phenyl	30	94
g	4-$MeOC_6H_4$	Phenyl	60	95
h	C_6H_5	4-ClC_6H_4	60	96
i	4-HOC_6H_4	4-ClC_6H_4	15	87

Various functionalities present in the aryl aldehydes, such as halogen, methoxy, hydroxyl, cyano, and nitro groups were tolerated (see Table 1). In all these cases, the corresponding α-aminophosphonates were obtained in good yields at room temperature without formation of any side products such as α-hydroxyphosphonate. It is important to note that the synthesis of α-aminophosphonates could not be achieved in the absence of catalyst (boric acid).

The mechanism of this reaction is believed to involve formation of an activated imine by the acidic catalyst so that addition of the phosphite is facilitated to give a phosphonium intermediate, which then undergoes reaction with the water generated during formation of the imine to give the α-aminophosphonate and methanol as shown in Scheme 2 [17,29].

In conclusion, this paper describes a convenient and efficient process for the synthesis of α-aminophosphonates by one-pot reaction of trimethyl phosphite, aldehydes, and amines in the presence of



SCHEME 2 Proposed mechanism.

10 mol% of boric acid at room temperature under solvent-free conditions. This method offers some advantages in terms of simplicity of performance, low reaction times, solvent-free condition, low cost, and it follows along the line of green chemistry. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. We believe that this procedure is convenient, economical, and a user-friendly process for the synthesis of α-aminophosphonates of biological and medicinal importance.

EXPERIMENTAL

General Procedures for Preparation of α-Aminophosphonates

A mixture of aldehyde (1 mmol) boric acid (10 mol%), amine (1 mmol), and trimethyl phosphite (1 mmol) was stirred at room temperature for the appropriate time as indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/*n*-hexane = 1/4). After completion of the reaction, the reaction mixture was diluted with water and extracted with chloroform, dried over Na_2SO_4, and concentrated under vacuum, and the crude mixture was purified by short column chromatography on silica gel eluting with ethyl acetate/*n*-hexane to afford pure products. Spectral data for selected product is presented below.

Compound **4a**: white solid, mp 87°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (d, $J = 10.5$ Hz, 3H), 3.81 (d, $J = 10.6$ Hz, 3H), 4.82 (d, $J = 24$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 2H), 6.74 (t, $J = 7.2$ Hz, 1H), 7.10 (t, $J = 7.7$ Hz, 2H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.50 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.1 (d, $^2J_{P-C} = 7.0$ Hz, OCH_3), 54.2 ($^2J_{P-C} = 6.8$ Hz, OCH_3), 56.2 (d, $^1J_{P-C} = 150$ Hz, CH), 114.3 (CH), 119.0 (CH), 128.2 (d, $^3J_{P-C} = 5.8$ Hz, CH), 128.4 (d, $^3J_{P-C} = 3.1$ Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, $^2J_{P-C} = 14.5$ Hz, C).

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